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Original article

Characterization of patients with duplicated z-hypnotic use: A population-based study in Taiwan

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ABSTRACT

Background/Purpose: A significant increase in the prescribing of nonbenzodiazepine hypnotic agents (z-hypnotics) has been noticed in the past decade. Several safety concerns have emerged after the excessive use of z-hypnotics. This study aims to characterize the z-hypnotics users with a focus on those with overlapping duration of z-hypnotics supply by using Taiwan's National Health Insurance Research Database.

Methods: Incident z-hypnotic users who received at least one z-hypnotic prescription from outpatient settings during 2001–2010 were identified and classified into three groups: duplicated users (those who received multiple z-hypnotic prescriptions on the same day), suspected duplicated users (those who received multiple z-hypnotic prescriptions with 7+ days of overlapping supply), and nonduplicated users. We examined the demographic profiles of these z-hypnotic users as well as z-hypnotics prescriptions (duration, daily consumption, and characteristics of providers).

Results: We identified 242,412 incident users of z-hypnotics with 2.4 million z-hypnotic prescriptions during the 10-year study. Almost 20% of them were duplicated (n = 29,948) and suspected duplicated users (n = 16,899). Duplicated and suspected duplicated users were more likely to be male and in their old age compared to the nonduplicated users. Approximately half of the suspected duplicated users (51.8%) and nonduplicated users (47.0%) received their z-hypnotic prescriptions from primary care clinics while duplicated users received their z-hypnotic prescriptions from metropolitan hospitals (29.9%) and academic medical center (26.2%). Duplicated z-hypnotic users were more likely to receive more days' supply and higher daily dose of z-hypnotics. Up to 31.0% of duplicated z-hypnotics users received > 1 defined daily dose/day if adding all prescriptions they received within 1 day.

Conclusion: Duplicated z-hypnotic users were more likely to receive prescriptions with long duration and high daily dose. Healthcare professionals and policy makers are recommended to put more efforts into dealing with this urgent drug safety issue.

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Introduction

A significant increase in the prescribing of nonbenzodiazepine hypnotic agents, the so-called *z-hypnotics*, has been noticed in the past decade.[1–4] Compared to benzodiazepines (BZDs), z-hypnotics are considered as safer alternatives for insomnia due to their improved pharmacokinetic profile.[5] However, several safety concerns have emerged after the tremendous use of z-hypnotics. Some

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studies have reported a high prevalence of inappropriate use of z-hypnotics, particularly long-term use in the elderly, which may result in adverse events.[1,6] Another major safety issue is the *doctor-shopping* behaviors among insomnia patients and accompanying dependency of z-hypnotics.[7] More empirical data regarding the quality of z-hypnotics prescriptions and characteristics of potential z-hypnotic-dependent users will help clinicians and policy-makers to identify *hot-spots* for rational use of z-hypnotics. Using Taiwan's National Health Insurance research database (NHIRD), this study examined the demographic profiles of z-hypnotic users as well as z-hypnotic prescriptions (duration and daily consumption) they received.

Methods

Data source

This retrospective cohort study used 12 years of data (1999–2010) from the National Health Insurance Research Database (NHIRD), a nationwide claims database from Taiwan's mandatory National Health Insurance program. The NHIRD contains anonymous eligibility and enrollment information, as well as claims for visits, procedures, and prescription medications for > 99% of the entire population (23 million) in Taiwan.[8] Two subsets of the NHIRD, the Longitudinal Health Insurance Database (LHID) 2000 and LHID 2005, which contains a total of two million beneficiaries randomly selected from the NHIRD were used as our original cohort. The details of LHIDs and NHIRD were described in the NHI website and in our previous publication.[1,9]

Study participants

Patients who received a prescription of z-hypnotics (zolpidem, zopiclone, or zaleplon) from an outpatient setting from January 1, 2001 to December 31, 2010 were identified as our study participants. The first prescription date of z-hypnotics was defined as the cohort entry date. To be eligible for the definition of incident z-hypnotics users, those who received z-hypnotics 1 year prior to the cohort entry date were excluded. The characteristics of z-hypnotic users were collected at the cohort entry date.

All z-hypnotic prescriptions received by our study participants in the outpatient setting between the cohort entry date and December 31, 2010 were retrieved from the LHID. Incident z-hypnotic users were then categorized into three groups based on how they received their z-hypnotic prescriptions. Those who ever received z-hypnotics on the same day were defined as the duplicated users while those who ever received z-hypnotics with ≥ 7 days of overlapping supply were defined as suspected duplicated users. For example, if a patient receives two prescriptions (both were 28-days of supply of z-hypnotic) on January 14 and January 26, respectively, then they are defined as the suspected duplicated user. Other z-hypnotic users were defined as nonduplicated users.

Measurements and statistical analysis

Demographics of z-hypnotic users including age and sex were collected. Providers' characteristics, including prescribing physicians and medical facilities, were further examined. Prescribing physicians were grouped by their specialties (e.g., psychiatry). Medical facilities were characterized by accreditation levels: medical center, metropolitan hospital, local community hospital, and clinic. Several measures, including prescription duration, daily pills, and daily dosage, were used to quantify the use of z-hypnotics among the three types of z-hypnotics users. The daily dosage of z-hypnotics was calculated by number of pills taken and defined daily dose (DDD) and presented by per-prescription as well as per-patient. The numbers of z-hypnotics prescriptions received within a day by duplicated z-hypnotics users were also investigated.

All data are expressed as number with percentage or mean with standard deviation and compared using analysis of variance (ANOVA) or Chi-square test. The analyses were performed with SAS, version 9.2 (SAS Institute, Cary, NC, USA).

Results

We identified 242,412 z-hypnotic users and 2.4 million z-hypnotic prescriptions received by them over the 10 years of the study period. The characteristics of z-hypnotic users are shown in Table 1. Nearly one-fifth of z-hypnotic users (n = 46,847) had received at least one duplicated or suspected duplicated prescriptions during the study period. The proportion of men in duplicated (41.2%) and suspected duplicated z-hypnotic users (41.0%) were significantly higher than nonduplicated users ($p < 0.01$). Approximately one-third (31.6%) of duplicated and one-fourth (26.8%) of suspected duplicated z-hypnotic users were elderly.

Duplicated z-hypnotic users received higher number of z-hypnotics prescriptions (36.1 prescriptions/patient in average) compared to the other two groups. Duplicated z-hypnotic users were more likely to receive their z-hypnotic prescriptions from metropolitan hospitals (29.9%) and medical centers (26.2%), whereas other users mostly received their z-hypnotics from clinics (47.0% in nonduplicated and 51.8% in suspected duplicated z-hypnotic users). Duplicated z-hypnotic users were more likely to receive their z-hypnotics prescriptions from neurology specialist but less likely from physicians in internal medicine and family medicine compared to the other two groups (Table 2).

Approximately 90% of duplicated z-hypnotics users received a prescription of > 7 days of supply (89.0% of 8–30 days and 0.5% of > 30 days). The daily z-hypnotic consumption was higher among duplicated users. Nearly one-sixth (15.2%) of them received > 1 DDD/d per prescription (vs. 6.8% of nonduplicated and 12.9% of suspected duplicated z-hypnotic users). Up to 31.0% of duplicated z-hypnotics users received > 1 DDD/d if adding all prescriptions they received within 1 day (Table 3).

Approximately 60% (56.9%) and 40% (42.4%) of duplicated z-hypnotic users received two or three prescriptions within a day. However, we found that very few patients received more than three z-hypnotics prescriptions within 1 day (Table 4).

Discussion

This study is the first to investigate the characteristics of duplicated z-hypnotics users and their utilization patterns of z-hypnotics over the past decade in Taiwan. We found that duplicated z-hypnotics users were more likely to be male and of older age and to receive their z-hypnotic prescriptions from metropolitan hospitals and medical centers. In addition, duplicated z-hypnotic users were more likely to receive prescriptions with long duration and high daily dose compared to their nonduplicated counterparts.

Recently, potential drug abuse resulting from multiple providers and drug-driven shopping behavior has become a critical issue in many countries.[10–12] Nevertheless, previous studies have focused on opioids but not in sedatives such as BZD and z-hypnotics. Identifying patients who have high possibility of duplicated z-hypnotics use can help to reduce the risks of z-hypnotic misuse and associated adverse events.

Under the universal healthcare insurance provided by Taiwan's National Health Insurance program, patients in Taiwan have very high accessibility to healthcare services with relatively low financial and referral barriers. It was estimated that 17.3% of outpatients

Table 1
Baseline characteristics of z-hypnotic users.

	Nonduplicated users	Suspected duplicated users	Duplicated users	p *
Patients number	195,565	16,899	29,948	
Sex				
Male	77,103 (39.5)	6,928 (41.0)	12,352 (41.2)	< 0.01
Female	118,104 (60.5)	9,955 (59.0)	17,574 (58.7)	
Age (y)	47.8 ± 17.3	51.9 ± 17.0	55.0 ± 16.2	< 0.01
< 18	2,774 (1.4)	92 (0.5)	102 (0.3)	< 0.01
18–39	64,621 (33.0)	4,208 (24.9)	5,497 (18.4)	
40–64	90,427 (46.2)	8,075 (47.8)	14,902 (49.8)	
65–79	30,191 (15.4)	3,700 (21.9)	7,837 (26.2)	
≥ 80	7,552 (3.9)	824 (4.9)	1,610 (5.4)	

Data are presented as n (%) or mean ± standard deviation.
* Analysis of variance or Chi-square test.

Table 2
Characteristics of z-hypnotics prescriptions received by non-, suspected-, and duplicated z-hypnotic users.

	Nonduplicated users (n = 195,565)	Suspected duplicated users (n = 16,899)	Duplicated users (n = 29,948)	p *
Prescriptions number	905,935	445,137	1,081,017	
Prescription/patient	4.6	26.3	36.1	
Setting				
Clinic	425,843 (47.0)	230,696 (51.8)	318,117 (29.4)	< 0.01
Local community hospital	151,053 (16.7)	75,583 (17.0)	156,395 (14.5)	
Metropolitan hospital	192,067 (21.2)	82,362 (18.5)	323,288 (29.9)	
Medical center	136,972 (15.1)	56,496 (12.7)	283,217 (26.2)	
Specialty				
Psychiatry	220,529 (24.3)	111,833 (25.1)	266,019 (24.6)	< 0.01
Family medicine	160,791 (17.7)	91,276 (20.5)	150,514 (13.9)	
Interior medicine	146,038 (16.1)	76,328 (17.1)	142,120 (13.1)	
Neurology	55,692 (6.1)	25,030 (5.6)	101,255 (9.4)	
Duration (d)	2.5 ± 0.7	2.7 ± 0.6	2.9 ± 0.5	< 0.01
< 3	135,431 (14.9)	31,884 (7.2)	41,372 (3.8)	< 0.01
3–7	175,603 (19.4)	50,477 (11.3)	73,013 (6.8)	
8–30	593,068 (65.5)	360,911 (81.1)	961,734 (89.0)	
> 30	1,833 (0.2)	1,865 (0.4)	4,898 (0.5)	

Data are presented as n (%) or mean ± standard deviation.
* Analysis of variance or Chi-square test.

Table 3
Comparison of daily consumption of z-hypnotics received by non-, suspected-, and duplicated z-hypnotic users.

	Nonduplicated users (n = 195,565)	Suspected duplicated users (n = 16,899)	Duplicated users (n = 29,948)		p *
	Per prescription	Per prescription	Per prescription	Per day	
Daily use (pills)	2.0 ± 0.6	2.1 ± 0.8	2.2 ± 0.8	2.6 ± 1.1	< 0.01
< 0.5	126,250 (13.9)	48,647 (10.9)	128,333 (11.9)	68,171 (8.0)	< 0.01
0.5–1	717,182 (79.2)	338,994 (76.2)	787,717 (72.9)	518,213 (60.9)	
1–1.5	12,989 (1.4)	11,002 (2.5)	33,047 (3.1)	34,637 (4.1)	
1.5–2	43,744 (4.8)	43,482 (9.8)	121,219 (11.2)	148,283 (17.4)	
> 2	5770 (0.6)	3062 (0.7)	10,701 (1.0)	80,981 (9.4)	
Daily dosage					< 0.01
≤ 1 DDD	843,939 (93.2)	387,870 (87.1)	916,614 (84.8)	587,022 (69.0)	
> 1 DDD	61,996 (6.8)	57,267 (12.9)	1,644,403 (15.2)	263,263 (31.0)	

Data are presented as n (%) or mean ± standard deviation.
* Analysis of variance or Chi-square test.
DDD = defined daily dose.

Table 4
Frequency of duplicated prescriptions within a day.

Prescription number	Patient number (%)
2	90,986 (56.9)
3	67,795 (42.4)
4	843 (0.5)
5	108 (0.1)
6–9	229 (0.1)
10+	2 (0.0)
Total	159,963

had visited different healthcare facilities on the same day in Taiwan.[13] This phenomenon is particularly prevalent in older patients, who usually have multiple comorbidities and tend to seek treatments from different specialties.[14] Our study also found that 12.3% of our study participants received more than two z-hypnotic prescriptions within a day. These duplicated z-hypnotic users were more likely to be older, which is consistent with findings from a study done by Wu et al[15] that there is an increasing risk for multiple physician visits associated with age. The risk of duplicated z-hypnotics use in the elderly could worsen if a patient repeatedly

complains of sleep problems when visiting different physicians in different medical institutions. A comprehensive review of medication use of a patient, especially an older one, is warranted to reduce such risk.

Our study also found significant variations in the distribution of sex and age among different types of z-hypnotic users. Women accounted for the majority of the entire z-hypnotic users; that is, women were more likely to receive z-hypnotics compared to men.[2,16,17] However, an increasing proportion of men was found among patients with duplicated z-hypnotic use. This finding is similar with a Norwegian population-based study, which suggested that inappropriate use of z-hypnotic and anxiolytic BZD in the elderly, defined as long-term use of z-hypnotics for > 30 weeks or use of z-hypnotics with high dosage, is more prevalent in men.[16] By contrast, another study conducted in general Danish elderly reported that women are more likely to receive long-term use of z-hypnotic, but the association become insignificant after limiting the analysis to z-hypnotic users only. The authors concluded that women are more likely to start z-hypnotics, but there is no difference in terms of long-term use of z-hypnotic between men and women.[6]

According to the results of our previous study, the proportion of z-hypnotic prescriptions from clinics and physicians not specializing in psychiatry were increased recently, raising the awareness of the easier access of z-hypnotics obtainment in Taiwan.[1] However, we found that patients with duplicated prescriptions were more likely to receive their prescriptions from physicians in psychiatry and tertiary-care hospitals. Patients' own comorbidities may be one of influential factors for these inconsistent results. For some diseases, combined use of psychotropic medications with lower level are recommended for reducing the risk of adverse drug effects. One cross-sectional study showed that psychotropic polypharmacy, which is defined as simultaneous use of two or more anxiolytic hypnotics, accounted for almost 70% of all person-days of anxiolytic-hypnotic use in Taiwan.[3] In addition, patients with mental diseases may be one of the reasons inducing multiple *opinion-seeking* or *drug-driven* visits. According to the study done by Norton et al,[18] doctor-shopping was associated with higher rates of mental illness. A study by Huang and Lai[19] also reported a significant association of concomitant anxiety or depression with higher consumption of hypnotics among older insomniacs. Indications and concomitant medication use among z-hypnotics users were beyond the investigation of this study and more research is warranted.

We found that duplicated z-hypnotic users were more likely to have higher and longer consumption of z-hypnotic compared to nonduplicated users. This finding was consistent with another Taiwanese study done by Lu et al,[7] which reported 736.49 DDD in patients with doctor-shopping behavior (defined as duplicated z-hypnotics with $\geq$ 1 overlapping day of supply from different physicians) and 160.63 DDD in those without during a 2-year follow-up period. Lu et al[7] also reported that only 20% of total z-hypnotics DDD among doctor-shopping patients originated from duplicated prescriptions. They concluded the potential tolerance of z-hypnotics triggers the needs for chronic and high-amount use. Our study further provided the details of total consumption per day and found that up to 31.0% of duplicated z-hypnotics users received > 1 DDD/d if adding all prescriptions they received within 1 day.

Our study adds to the knowledge regarding the characteristics of duplicated z-hypnotics users and their utilization patterns of z-hypnotics. Nevertheless, there were several limitations in this study. First, as with all observational studies based on claim databases, we were unable to include social and behavior factors associated with duplicated z-hypnotic users. Second, the total amount of z-hypnotic use by our study participants may be underestimated as patients may receive their z-hypnotics from other sources.

In summary, duplicated z-hypnotic users were more likely to receive prescriptions with long duration and high daily dose compared to their nonduplicated counterparts. Healthcare professionals and policy makers are recommended to invest more effort in dealing with this urgent drug safety issue.

Conflicts of interest

All authors have no conflicts of interest to declare.

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